REMARKS

Claims 8, 10, 11, 16, 26, 28, 29 and 37-42 were pending in the application. Claim 37 has been amended. New claims 43-48 have been added. Accordingly, claims 8, 10, 11, 16, 26, 28, 29 and 37-48 are now pending.

Support for new claims 43 and 48 can be found throughout the specification, including at least at page 18, lines 28-30 and at page 25, Table II. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Previous Rejection of Claims Under 35 U.S.C. § 112, first paragraph

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 8, 16 and 18, 19, 26, 27 and 39 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims Under 35 U.S.C. §102(b)

I. *Rejection of Claims 8, 10, 26-28, 39, 40, and 42 Under 35 U.S.C. §102(b) in view of Crowe et al.*

The Examiner has rejected claims 8, 10, 26-28, 39, 40, and 42 as being anticipated by Crowe *et al.* (1994) *Science* 264:707 (hereinafter Crowe-Science). The Examiner states that "the process of making the product in this case does not impart any structurally distinct characteristics that would help distinguish this product over that of the prior art." Applicants respectfully traverse this rejection.

Under 35 U.S.C. 102, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Furthermore, "the identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Applicants respectfully submit that the Examiner has failed to establish how Crowe-Science teaches each and every element of the claimed invention in accordance with 35 U.S.C. §102.

The claimed invention is directed to a preparation ***comprising at least 70% biologically active*** receptor-immunoglobulin fusion protein (receptor-Ig-fusion protein), obtained by culturing a mammalian host cell transformed with DNA encoding the receptor-Ig fusion protein in a culture system having a temperature of about 27° C to about 35° C, wherein the receptor-Ig fusion protein comprises a member of the TNF family of receptors. In contrast, Crowe-Science describes a preparation comprising ***50% biologically active*** LT-β-R-Ig fusion proteins made according to standard culture conditions (see page 16, lines 6-7 of instant specification). The claimed invention also describes a preparation comprising a biologically active receptor-Ig-fusion protein (comprising a member of the TNF family of receptors) obtained by culturing yeast transformed with DNA encoding the receptor-Ig-fusion protein in a culture system having a temperature of about 10° C to about 25° C. Crowe-Science describes $TNFR_{60}$:Fc, $TNFR_{80}$:Fc, and $TNFR_{rp}$:Fc fusion proteins which are expressed in mammalian cells or baculovirus according to standard culturing conditions (see

Crowe *et al.*, Mohler *et al.*, and Farlow *et al.* cited as references 12, 26, and 27, respectively, in Crowe-Science at page 709, column 3, no. 7) which result in 50% biologically active proteins evidenced by the working examples of the instant specification.

Applicants respectfully point out that the instant invention is not directed to an isolated biologically active TNF receptor fusion protein, but instead to a preparation comprising at least 70% biologically active molecules. The claimed preparation is not anticipated by Crowe-Science, as the preparation described in Crowe-Science does not comprise at least 70% biologically active TNF receptor-Ig fusion proteins. The distinction between the claimed preparation and the preparation described in Crowe-Science is exemplified in Figure 9 of the specification. Figure 9 shows results measuring the percentage of inactive LT-β-R-Ig fusion in preparations obtained under conventional culturing conditions like those used in Crowe-Science, *i.e.,* 37° C, in contrast to the low percentage of inactive proteins found in preparations obtained from cell cultures grown at lower temperatures, *i.e.,* 27° C to 35° C. As shown in Figure 9, the preparations of the instant invention are distinct from the preparations of LT-β-R-Ig fusion proteins described in Crowe-Science as each preparation contains a unique composition of active versus inactive molecules.

The Crowe-Science reference fails to anticipate the claimed invention because there is no evidence presented in Crowe-Science that the described preparations comprise an increased yield of biologically active TNF receptor fusions proteins. As described above and in Applicants' previous responses, the specification provides working examples which demonstrate that culturing TNF receptor fusions proteins using conventional conditions in the art, *i.e.,* those used in Crowe-Science, results in a preparation comprising a decreased yield of biologically active TNF receptor fusion proteins. Applicants teach that culturing TNF receptor fusion proteins using a low temperature culture method results in a preparation comprising an increased yield, *e.g.,* at least 70% biologically active TNF receptor fusions proteins. Crowe-Science does not teach each and every element of the claimed invention, and, therefore, Crowe-Science does not anticipate the claimed preparations. Applicants respectfully request that the rejection under 102(b) in view of Crowe-Science be withdrawn.

II. *Rejection of Claims 8, 11, 26, 29, 37-40, and 42 Under 35 U.S.C. §102(b) in view of Kwon et al.*

The Examiner has rejected claims 8, 11, 26, 29, 37-40, and 42 as being anticipated by Kwon *et al.* (1997) *J. Biol. Chem.* 272:14272 (hereinafter Kwon). The Examiner states, "the product taught by Kwon *et al.* appears to have the same activity of the instant product (i.e. ability to bind to a ligand) and therefore the claim limitations drawn to means of preparing the product do not necessarily impart any structurally distinct characteristics onto the claimed product." Applicants respectfully traverse the rejection in view of Kwon.

As described in Applicants' previous response of September 27, 2004, the Kwon reference teaches the identification and characterization of the TNF receptor family member TR2 and describes expression of a TR2-Fc fusion protein in NIH 3T3 cells and CHO cells. The authors of the Kwon reference do not describe (or provide any motivation to make) deviations from conventional protein expression protocols in their Materials and Methods section. As discussed above and in Applicants' previous response, Applicants have shown that standard culture conditions result in a preparation having substantially fewer active molecules than the claimed preparations. Accordingly, the Kwon reference does not teach each and every element of the claimed invention as required under 35 U.S.C. § 102.

In contrast to the Examiner's assertion, the claim limitations drawn to a means of preparing the claimed preparation do impart distinct characteristics onto the claimed product. As required by the claims and described in the specification at page 11, lines 16-21 and 27-29, the claimed invention provides a preparation comprising highly enriched biologically active TNF receptor-Ig fusions proteins. In contrast, the preparation described in Kwon comprises a low level of biologically active TR2-Fc fusion proteins as the preparation is not obtained according to the process determined by Applicants and described in the specification. Kwon fails to teach or suggest each and every element of Applicants' invention, and, therefore, Applicants respectfully request that the rejection of claims 8, 11, 26, 29, 37-40, and 42 under §102(b) over Kwon be reconsidered and withdrawn.

III. *Rejection of Claims 8, 10, 16, 26, 28, and 39-42 Under 35 U.S.C. §102(b) in view of Rennert et al.*

The Examiner has rejected claims 8, 10, 16, 26, 28, and 39-42 as being anticipated by Rennert *et al.* (1996) *J. Exp. Med.* 184:1999 (hereinafter Rennert). The Examiner states, "Rennert *et al.* teach a product that is identical to that instantly claimed and applicant has not provided objective evidence to show structure [sic] difference between the prior art and that instantly claimed." Applicants respectfully traverse this rejection.

As described by Applicants previously, the Rennert reference describes injection of either an LT-β-R-Ig or a TNFR55-Ig fusion protein into pregnant mice to in an effort to distinguish the role of the LT and TNF pathways during embryonic development. Rennert cites references for protocols regarding expression of the receptor-Ig fusion proteins, none of which teach or suggest expression of Ig fusion proteins using a protocol which deviates from conventional standards. Again, as discussed above, Applicants have shown that standard culture conditions result in a preparation having substantially fewer active molecules than the claimed preparations.

In contrast to the Examiner's assertion, the Rennert reference does not teach a preparation which is identical to that instantly claimed. The claimed preparation comprises a high percentage of active molecules, while the preparation described in the Rennert reference contains a lower percentage of active molecules than those claimed. Furthermore, Applicants have provided objective evidence to show the differences between the cited art and the claimed invention. As described above and Applicants previous responses, Applicants provide working examples in the specification which demonstrate that preparations comprising TNF receptor-Ig fusion proteins obtained from cell cultures grown at temperatures lower than those used conventionally in the art have an increased percentage of biologically active proteins. Applicants also previously provided objective evidence regarding standard temperatures in the art, including protocols from molecular biology lab textbooks which describe protein expression in mammalian cells.

Claim 16 is directed to a pharmaceutical preparation obtained using Applicants' low temperature method of culturing, wherein the LT-β-R-Ig fusion protein is recovered from the

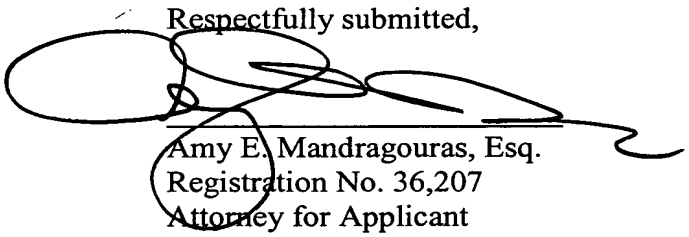
host cell and combined with a pharmaceutically acceptable carrier. According to 35 U.S.C. 102, Rennert must teach each and every element of the claimed invention in order to anticipate claim 16. In addition to not teaching a preparation obtained by lowering host cell culturing conditions, a required element of claim 16, the Rennert reference also does not teach a pharmaceutical preparation comprising an LT-β-R-Ig fusion protein. Thus, the invention of claim 16 is not anticipated by Rennert.

In sum, because Rennert fails to teach or suggest each and every element of Applicants' invention, Applicants respectfully request that the rejection of claims 8, 10, 16, 26, 28, and 39-42 under §102(b) over Rennert be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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